510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
DEVICE AND INSTRUMENT TEMPLATE

A. 510(k) Number:
k033155

B. Analyte:
Cardiac Troponin I, Creatine Kinase-MB (CK-MB), and Myoglobin

C. Type of Test:
Quantitative immunoassay

D. Applicant:
BioCentrex

E. Proprietary and Established Names:
BioCentrex Cardiac Panel

F. Regulatory Information:

1. Regulation section:
   21 CFR § 862.1215, Creatine phosphokinase/Creatine kinase or isoenzymes test system
   21 CFR§ 866.5680, Myoglobin Immunological Test System
2. Classification:
   Class II
3. Product Code:
   MYT, Biosensor, Immunoassay, Cpk or Isoenzyme
   MMI, Immunoassay method, troponin subunit
   DDR, Myoglobin Immunological test system
   JHX, Fluorometric Method, Cpk or Isoenzymes
4. Panel:
   Clinical Chemistry (75) and Immunology (82)

G. Intended Use:

1. Indication(s) for use:

   The BioCentrex Cardiac Panel cartridge is intended for in vitro diagnostic use with the BioCentrex Analyzer to quantitatively measure cardiac Troponin I, Creatine kinase-MB, and myoglobin from whole blood, serum, or plasma specimens to aid in the diagnosis and treatment of patients with myocardial infarction.

2. Special condition for use statement(s):
   For in vitro diagnostic use

3. Special instrument Requirements:
   BioCentrex Analyzer

H. Device Description:

Each BioCentrex Cardiac Panel cartridge consists of a hemoglobin pad, a plastic waveguide, and lyophilized reagent cup. Mouse monoclonal antibodies to cTnI, CK-MB and myoglobin are spotted on the plastic waveguide while fluorescent-labeled mouse monoclonal antibodies to cTnI, CK-MB and myoglobin are contained in the lyophilized reagent cup. The user places the specimen in the Sample Tube Holder of the BioCentrex Analyzer, and places the Cardiac Panel cartridge on the Cartridge Drawer before initiating the test. Upon initiation of the test, the analyzer spots an aliquot of the specimen on the hemoglobin determination pad and then delivers another aliquot to the reagent cup to reconstitute and mix with the reagent. After a brief preincubation interval, the mixture is diluted with Wash/Diluent Solution before delivering the mixture to the waveguide.

I. Substantial Equivalence Information:

1. Predicate device name(s):
   Access® AccuTnI™ for Use on the Access® Immunoassay Analyzer
   Access® CK-MB for Use on the Access® Immunoassay Analyzer
   Access® Myoglobin for Use on the Access® Immunoassay Analyzer

2. Predicate K number(s):
   K021814
   K000716
   K951634
3. Comparison with predicate:

The device and its predicate share similar intended use, indications for use, method principle, reporting units, sample volume, reaction temperature, test time, and antibody types. Differences are listed below:

Differences		
Item	**Device**	**Predicate**
Instrument	BioCentrex Analyzer	Access analyzer
Detection method	Fluorescence detection on a planar waveguide	Chemiluminescent enzyme imunoasay
Signal detection	CCD camera	luminometer
Sample type	Anti-coagulated whole blood, serum, or plasma	Serum or plasma
Calibration	Bar-coded, stored lot calibration	6 levels of liquid calibrators
Detection limit	TnI: 0.15 ng/mL CK-MB: 0.41 ng/mL Myo: 2.8 ng/mL	TnI: 0.01 ng/mL CK-MB: 0.3 ng/mL Myo: 8.9 ng/mL
Reportable range	TnI: 0.15 - 100 ng/mL	TnI: 0.01 – 100 ng/mL

	CK-MB: 0.41 - 250 ng/mL Myo: 2.8 - 400 ng/mL	CK-MB: 0.3 - 300 ng/mL Myo: 8.9 – 4000 ng/mL
Reference Interval	TnI: <0.15 ng/mL (97.5th URL) CK-MB: 0.41 – 5.7 ng/mL Myo: 8.2 – 101.5 ng/mL	TnI: 0.03 ng/mL (URL) CK-MB: 0.3 – 4.0 ng/mL Myo: 70 ng/mL (URL)

J. Standard/Guidance Document Referenced (if applicable):

NCCLS Guideline EP5-A - Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline

NCCLS Guideline C28-A - How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline

NCCLS Guideline EP7-A - Interference Testing in Clinical Chemistry; Proposed Guideline

NCCLS Guideline EP9-A2 - Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline

NCCLS Guideline EP6-P2 - Evaluation of the Linearity of Quantitative Analytical Methods

NCCLS Guideline I/LA21-A - Clinical Evaluation of Immunoassays; Approved Guideline

K. Test Principle:

To determine the hematocrit of an anti-coagulated whole blood specimen, wavelength-specific light from a light emitting diode is reflected off the bottom of the hemoglobin pad and measured by two photodiodes mounted in the analyzer. The analyzer uses the reflectance measurements and a standard curve from the cartridge barcode to calculate the hematocrit of the whole blood sample. The estimated hematocrit is then used to correct for variations in plasma volumes in whole blood samples.

CTnI, CK-MB and myoglobin in the sample complex with analyte-specific fluorescent-labeled antibody in the reagent and the capture antibody spotted on the waveguide. Fluorescence is generated upon excitation by the evanescent wave, which propagates through the planar waveguide. The fluorescence concentration at the capture site is greater than the background fluorescence in the bulk solution so bound fluorescence is not separated from free fluorescence. The course of this binding reaction is measured 77 times over an 8-minute period using a CCD camera to monitor the fluorescence of each spot as it develops. After the 8 minutes the rate of the reaction is compared to the stored calibration curve, and corrected for hematocrit for conversion of cTnI, CK-MB and myoglobin concentrations to ng/mL, which is then displayed on the analyzer. The fluorescence rate is directly proportional to the concentration of cTnI, CK-MB and myoglobin in the specimen.

L. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>
    a. Precision/Reproducibility:

Within-run, between-run, and total imprecision were determined following NCCLS Guideline EP5-A. Three human serum-based controls (two commercial and one in-house) containing three levels of cardiac Troponin I were tested in duplicate. Results are summarized below:

Troponin I – 20 runs over 10 days:

		Within-run		Between-run		Between-day		Total	
	Mean	**SD**	**CV**	**SD**	**CV**	**SD**	**CV**	**SD**	**CV**
Level 1	0.74	0.03	4.5 %	0.02	2.7 %	0.05	6.4 %	0.06	8.3 %
Level 2	2.002	0.07	3.1 %	0.06	3.1 %	0.03	1.6 %	0.10	5.8 %
Level 3	7.74	0.37	4.7 %	0	0 %	0.23	5.3 %	0.43	5.6 %

CK-MB – 20 runs over 10 days:

		Within-run		Between-run		Between-day		Total	
	Mean	**SD**	**CV**	**SD**	**CV**	**SD**	**CV**	**SD**	**CV**
Level 1	3.63	0.28	7.8 %	0.16	4.4 %	0	0 %	0.32	8.9 %
Level 2	24.7	1.82	7.4 %	0.33	1.4 %	0	0 %	1.85	7.5 %
Level 3	109.9	7.0	6.3 %	4.1	3.7 %	2.5	2.3 %	8.4	7.7 %

Myoglobin – 40 runs over 20 days:

		Within-run		Between-run		Between-day		Total	
	Mean	**SD**	**CV**	**SD**	**CV**	**SD**	**CV**	**SD**	**CV**
Level 1	36.0	2.20	6.1 %	0	0 %	1.23	3.4 %	2.52	7.0 %
Level 2	163.4	11.5	7.0 %	2.87	1.8 %	2.37	1.4 %	12.1	7.4 %
Level 3	376.2	28.4	7.5 %	0	0 %	7.49	2.0 %	29.3	7.8 %

Duplicate measurements of serum samples were compared to determine validity of performing single measurements. The following results were obtained:

Troponin I: $y = 0.9684x + 0.1144$
$r = 0.9972$; $R^2 = 0.9945$
$n = 76$
Range = 0 to 99 ng/mL

CK-MB: $y = 1.0161x – 0.7008$
$r = 0.9979$; $R^2 = 0.9958$
$n = 76$
Range = 2.88 to 365 ng/mL

Myoglobin: $y = 1.0247x – 3.2108$
$r = 0.9951$; $R^2 = 0.9903$
$n = 70$
Range = 18 to 718 ng/mL

b. Linearity/assay reportable range:

Percent recovery was evaluated according to NCCLS Guideline EP6-P2. Multiple dilutions covering the measuring range were made of 3 spiked plasma samples using the respective un-spiked plasma. Each dilution was assayed in duplicate, and observed results were compared to expected (calculated) results. The overall mean recovery was 99.7 % of expected (Troponin I), 99.2 % of expected (CK-MB), and 100.9 % of expected (Myoglobin).

c. Traceability (controls, calibrators, or method):

The instrument is calibrated by repeated measurements of cardiac patient specimens that have been assigned analyte concentrations using commercially available assays.

Each lot of cartridges contains a bar-coded, stored lot calibration curve. The curve is generated using standards which are assigned values based on measurements using a master lot and master analyzer (calibrated as above). The calibration is verified by analyte controls which are also value assigned on the master instrument.

No user calibration is required.

d. Detection limit:

The Functional Sensitivity was determined for cTnI as the lowest concentration yielding a CV = 20%. This value was calculated from a regression fit as 0.15 ng/mL. The sponsor states that the instrument will not report results below 0.15 ng/mL.

The analytical sensitivity, defined as the concentration distinguishable from zero with a 95% confidence, is determined to be 0.04 ng/mL (Troponin I), 0.41 ng/mL (CK-MB), and 2.8 ng/mL (Myoglobin). This was measured as the mean signal of 20 replicates of the zero calibrator plus 2 standard deviations.

e. Analytical specificity:

Interference studies were performed according to NCCLS Guideline EP7-A. Seven pools of potential drug interferents were spiked into commercial serum controls for each analyte (2.05 ng/mL Troponin I, 25.6 ng/mL CK-MB, or 281 ng/mL myoglobin). No drug tested caused interference in the assay (interference was defined as a mean difference greater than 10% than experimental control).

The device was tested for interference by potentially cross-reacting endogenous proteins. Potentially interfering proteins were added to commercial serum controls containing the analyte (2.05 ng/mL Troponin I, 25.6 ng/mL CK-MB, or 281 ng/mL myoglobin) and to sodium heparin plasma samples (0 ng/mL Troponin I, 1.5 ng/mL CK-MB, or 17.0 ng/mL myoglobin), and analyte levels were assayed and compared to similarly diluted experimental controls. There was no cross-reactivity reported for any of the proteins tested.

Potential interference by endogenous substances (human serum albumin, Bilirubin, hemoglobin, and triglycerides) was tested in commercial serum controls containing the analyte (2.05 ng/mL Troponin I, 25.6 ng/mL CK-MB, or 281 ng/mL myoglobin) and in sodium heparin plasma samples (0 ng/mL Troponin I, 1.5 ng/mL CK-MB, or 17.0 ng/mL myoglobin). All serum control results were within 10% of the control. Hemoglobin (at 500 mg/dL) increased the apparent TnI concentration by 0.03 ng/mL, and Bilirubin (at 40.1 mg/dL) increased the apparent TnI concentration by 0.1 ng/mL. In both cases, the original TnI concentration was below 0.5 ng/mL and the functional sensitivity of the assay. All other plasma sample results were within 10% of the control.

f. Assay cut-off:
Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison was performed between the device and the predicate according to NCCLS Guideline EP9-A2. Serum samples were assayed in duplicate on each device. Results are summarized below:

Troponin I: $y = 0.988x + 0.0879$
$r = 0.9885$; $R^2 = 0.9771$
$n = 77$
Range = 0 to 99 ng/mL
Std. error of the Estimate = 1.1163 ng/mL

CK-MB: $y = 0.995x + 0.313$
$r = 0.9949$; $R^2 = 0.9898$
$n = 70$
Range = 2.35 to 341 ng/mL
Std. error of the Estimate = 8.935 ng/mL

Myoglobin: $y = 0.9638x + 6.4649$
$r = 0.9852$; $R^2 = 0.9707$
$n = 70$
Range = 12 to 710 ng/mL
Std. error of the Estimate = 30.4 ng/mL

b. Matrix comparison:

Matched Heparinized whole blood vs. plasma:

	N	Range (ng/mL)	Slope	Intercept	r	R^2
Troponin I	11	0 to 26.6	1.0583	0.0009	0.9888	0.9777
CK-MB	11	0 to 174.6	0.9697	0.5499	0.9951	0.9903
Myoglobin	11	22.4 to 270.8	1.0054	1.3102	0.9796	0.9597

Matched Sodium heparin plasma vs. serum:

	N	Range (ng/mL)	Slope	Intercept	r	R^2
Troponin I	16	0 to 84.5	0.9468	-2.2177	0.9795	0.9594
CK-MB	19	2.7 to 168	1.1176	0.203	0.9942	0.9884
Myoglobin	19	52 to 342	0.9818	17.478	0.9689	0.9388

Heparin plasma vs. EDTA plasma:

	N**	Range (ng/mL) (spiked)	Slope	Intercept	r	R^2
Troponin I	1	0.01 to 7.14	1.293	-1.27	0.9985	NA*
CK-MB	1	1.0 to 72	1.075	1.27	0.9985	NA*
Myoglobin	1	12.5 to 264	1.023	1.62	0.9985	NA*

*NA = not addressed

**N = 1 sample spiked to 4 different levels

3. Clinical studies:
   - *a. Clinical sensitivity:*
     Not applicable.
   - *b. Clinical specificity:*
     Not applicable.
   - *c. Other clinical supportive data (when a and b are not applicable):*

4. Clinical cut-off:

The sponsor states that Troponin I levels greater than 0.5 ng/ml are consistent with WHO criteria for AMI. However, no supporting studies have been performed, so clinical laboratories must establish cutoffs that are appropriate for their representative populations.

5. Expected values/Reference range:

The reference interval was determined non-parametrically by testing serum samples from 120 male and 60 female apparently healthy individuals.

Troponin I: The central 95% interval was 0.0 to 0.07 ng/ml. The 97.5th percentile upper range limit (URL) of normals is <0.15 ng/mL (below the functional sensitivity).

CK-MB: The central 95% interval was 0.0 to 5.51 ng/mL. The reference interval (defined by the detection limit and the 97.5th percentile URL) is 0.41 to 5.51 ng/mL.

Myoglobin: The central 95% interval was 8.2 to 101.5 ng/mL for males and 4.5 to 42.2 ng/mL for females. The reference intervals (defined by the detection limit and the 97.5th percentile URL) of myoglobin are 2.8 to 42.2 ng/mL (females) or 2.8 to 101.5 ng/mL (males).

M. Instrument Name:

BioCentrex Analyzer

N. System Descriptions:

1. Modes of Operation:
   Open tube
2. Software:

OTS Software: Windows™ 98 SE, v.4.10.2222 (operating system – closed)
MathWorks Matlab 6.1 runtime libraries (data analysis)
Drivers for the hardware components

A graphical user interface allows the user to perform the testing and related functions by responding to a series of prompts on the screen.

FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:
Yes ✓ or No __:

3. Sample Identification:
   Patient ID information is entered manually.
4. Specimen Sampling and Handling:
   Analyzer uses anti-coagulated whole blood, serum, or plasma by direct open tube sampling
5. Assay Types:
   Immunoassays
6. Reaction Types:
   Fluorometric measurements
7. Calibration:
   Each lot of cartridges is calibrated via a bar-coded, stored lot calibration curve. The calibration can be verified using commercial material.
8. Quality Control:
   No provided QC material (use of commercial material recommended)

O. Other Supportive Instrument Performance Characteristics Data Not Covered In The "L. Performance Characteristics" Section Of the SE Determination Decision Summary.

Not applicable.

P. Conclusion:

I recommend that the BioCentrex Cardiac Panel is substantially equivalent to the legally marketed predicate device.